

## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

PHARMACIA ITALIA S.p.A./PATENT  
DEPARTMENT  
Viale Pasteur, 10  
I-20014 Nerviano  
ITALIE

Date of mailing (day/month/year) 11 February 2002 (11.02.02)	<b>IMPORTANT NOTIFICATION</b>
Applicant's or agent's file reference FC 879/5	
International application No. PCT/EP00/07679	International filing date (day/month/year) 03 August 2000 (03.08.00)

1. The following indications appeared on record concerning:	
<input checked="" type="checkbox"/> the applicant	<input type="checkbox"/> the inventor <input type="checkbox"/> the agent <input type="checkbox"/> the common representative
Name and Address PHARMACIA & UPJOHN S.P.A. Via Robert Koch, 1.2 I-20152 Milan Italy	State of Nationality IT
	State of Residence IT
	Telephone No. 390248 385216
	Facsimile No. 3902348 385397
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:	
<input type="checkbox"/> the person <input type="checkbox"/> the name <input type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence	
Name and Address PHARMACIA ITALIA S.p.A. Via Robert Koch, 1.2 I-20152 Milan Italy	State of Nationality IT
	State of Residence IT
	Telephone No. 390248 385216
	Facsimile No. 3902348 385397
3. Further observations, if necessary:	
4. A copy of this notification has been sent to:	
<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Anne BEUCHAT Telephone No.: (41-22) 338.83.38
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# INTERNET COOPERATION TREATY

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## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
US Department of Commerce  
United States Patent and Trademark  
Office, PCT  
2011 South Clark Place Room  
CP2/5C24  
Arlington, VA 22202  
ETATS-UNIS D'AMERIQUE  
in its capacity as elected Office

Date of mailing (day/month/year) 26 June 2001 (26.06.01)	
International application No. PCT/EP00/07679	Applicant's or agent's file reference FC 879/5
International filing date (day/month/year) 03 August 2000 (03.08.00)	Priority date (day/month/year) 16 September 1999 (16.09.99)
Applicant MUGGETTI, Lorena et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
06 April 2001 (06.04.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p>Authorized officer Olivia TEFY</p> <p>Telephone No.: (41-22) 338.83.38</p>
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# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>FC 879/5</b>	<b>FOR FURTHER ACTION</b> <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small>	
International application No. <b>PCT/EP 00/ 07679</b>	International filing date (day/month/year) <b>03/08/2000</b>	(Earliest) Priority Date (day/month/year) <b>16/09/1999</b>
Applicant  <b>PHARMACIA &amp; UPJOHN S.P.A.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.  
☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.     

- ☐ as suggested by the applicant.
- ☐ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.
- ☐ None of the figures.

Internal Application No  
PC/EP 00/07679

IPC 7	A61K9/08	A61K47/40	A61K31/565	A61P35/00	A61K31/66
	A61K47/42				

IPC 7 A61K

WPI Data, PAJ, CHEM ABS Data

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 09072 A (PHARMACIA) 28 March 1996 (1996-03-28) claims ---	1-24
A	US 5 804 568 A (J. RUBINFELD) 8 September 1998 (1998-09-08) cited in the application claims ---	1-24
A	US 5 134 127 A (V. STELLA ET AL.) 28 July 1992 (1992-07-28) cited in the application claims ---	1-24
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☒ Patent family members are listed in annex.

**'&' document member of the same patent family**

Scarponi, U

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 00/07679

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 98 51282 A (IMARX)  19 November 1998 (1998-11-19)  claims 1-7, 9-11, 29, 30, 74-76, 78, 79, 81-85  page 6, line 9 - line 15  page 10, line 1 - line 8  page 18, line 1 - line 14  page 19, line 19 - line 26  page 84, line 1 - line 14  page 96, line 16 - line 18</p> <p style="text-align: center;">----</p>	1-24
A	<p>WO 84 02270 A (AB LEO)  21 June 1984 (1984-06-21)  claims  page 5, line 12  examples 8,9</p> <p style="text-align: center;">-----</p>	1-24

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 00/07679

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9609072 A	28-03-1996	AU 698425 B	29-10-1998
		AU 3519995 A	09-04-1996
		CA 2174968 A	28-03-1996
		CN 1135719 A	13-11-1996
		CZ 9601456 A	14-08-1996
		EP 0730474 A	11-09-1996
		FI 962120 A	20-05-1996
		HU 75935 A	28-05-1997
		IL 115376 A	09-05-1999
		JP 9505832 T	10-06-1997
		NO 961979 A	14-05-1996
		NZ 292895 A	27-04-1998
		PL 314584 A	16-09-1996
		US 5712260 A	27-01-1998
		ZA 9507938 A	18-04-1996
US 5804568 A	08-09-1998	US 5602112 A	11-02-1997
		US 6048845 A	11-04-2000
		CA 2172159 A	09-03-1995
		EP 0717638 A	26-06-1996
		HU 73778 A	30-09-1996
		JP 9502185 T	04-03-1997
		AU 7718694 A	22-03-1995
		WO 9506485 A	09-03-1995
US 5134127 A	28-07-1992	AT 170742 T	15-09-1998
		AU 646020 B	03-02-1994
		AU 7236491 A	21-08-1991
		CA 2074186 A	24-07-1991
		DE 69130165 D	15-10-1998
		DE 69130165 T	29-04-1999
		EP 0512050 A	11-11-1992
		JP 2722277 B	04-03-1998
		JP 5504783 T	22-07-1993
		KR 166088 B	15-01-1999
		RU 2099354 C	20-12-1997
		WO 9111172 A	08-08-1991
		US 5376645 A	27-12-1994
WO 9851282 A	19-11-1998	AU 7378798 A	08-12-1998
		AU 7796198 A	08-12-1998
		EP 0983060 A	08-03-2000
		EP 0981333 A	01-03-2000
		WO 9851284 A	19-11-1998
WO 8402270 A	21-06-1984	JP 1000926 B	10-01-1989
		JP 1521010 C	29-09-1989
		JP 59108800 A	23-06-1984
		EP 0128186 A	19-12-1984

## PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING  
SUBMISSION OR TRANSMITTAL  
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

PHARMACAI & UPJOHN S.P.A./PATENT  
DEPARTMENT  
Viale Pasteur, 10  
I-20014 Nerviano  
ITALIE

Date of mailing (day/month/year) 02 October 2000 (02.10.00)	<b>IMPORTANT NOTIFICATION</b>
Applicant's or agent's file reference FC 879/5	
International application No. PCT/EP00/07679	International filing date (day/month/year) 03 August 2000 (03.08.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 16 September 1999 (16.09.99)
Applicant PHARMACIA & JOHN S.P.A. et al	

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- An asterisk(\*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
16 Sept 1999 (16.09.99)	9921954.5	GB	18 Sept 2000 (18.09.00)

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Eugénia Santos

Telephone No. (41-22) 338.83.38

# PATENT COOPERATION TREATY

30 MAR 2001

PCT

From the INTERNATIONAL BUREAU

To:

PHARMACIA & UPJOHN S.P.A./PATENT  
DEPARTMENT  
Viale Pasteur, 10  
I-20014 Nerviano  
ITALIE

## NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 22 March 2001 (22.03.01)		
Applicant's or agent's file reference FC 879/5		IMPORTANT NOTICE
International application No. PCT/EP00/07679	International filing date (day/month/year) 03 August 2000 (03.08.00)	
		Priority date (day/month/year) 16 September 1999 (16.09.99)
Applicant PHARMACIA & UPJOHN S.P.A. et al		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:

AU, KP, KR, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EA, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OA, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 22 March 2001 (22.03.01) under No. WO 01/19338

### REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

### REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38



Continuation of Form PCT/IB/308

**NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF  
THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES**

<b>Date of mailing (day/month/year)</b> 22 March 2001 (22.03.01)	<b>IMPORTANT NOTICE</b>
<b>Applicant's or agent's file reference</b> FC 879/5	<b>International application No.</b> PCT/EP00/07679
<p>The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.</p>	

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT PCT

(PCT Article 36 and Rule 70)

REC'D 25 SEP 2001

Applicant's or agent's file reference FC 879/5	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP00/07679	International filing date (day/month/year) 03/08/2000	Priority date (day/month/year) 16/09/1999
International Patent Classification (IPC) or national classification and IPC A61K9/08		
Applicant PHARMACIA & UPJOHN S.P.A. et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  06/04/2001	Date of completion of this report  21.09.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Graham, J  Telephone No. +49 89 2399 7368



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/07679

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):  
**Description, pages:**

1-13 as originally filed

### Claims, No.:

1-24 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
  - ☐ the language of publication of the international application (under Rule 48.3(b)).
  - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
  - ☐ filed together with the international application in computer readable form.
  - ☐ furnished subsequently to this Authority in written form.
  - ☐ furnished subsequently to this Authority in computer readable form.
  - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
  - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
4. The amendments have resulted in the cancellation of:
- ☐ the description, pages:
  - ☐ the claims, Nos.:
  - ☐ the drawings, sheets:
5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP00/07679

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims 1 - 24
	No: Claims
Inventive step (IS)	Yes: Claims 1 - 24
	No: Claims
Industrial applicability (IA)	Yes: Claims 1 - 22
	No: Claims

2. Citations and explanations  
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/EP00/07679

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

The following documents are referred to:

- D1: WO 96 09072 A (PHARMACIA) 28 March 1996 (1996-03-28)  
D2: US-A-5 804 568 (J.RUBINFELD) 8 September 1998 (1998-09-08) cited in the application  
D3: US-A-5 134 127 (V. STELLA ET AL.) 28 July 1992 (1992-07-28) cited in the application

**1.0 Novelty (Article 33(2) PCT)**

The subject matter of claims 1 to 22 is rendered novel since none of the prior art documents D1 to D3 disclose compositions comprising estramustine phosphate, a sulfoalkyl ether cyclodextrin and human albumin.

The above analysis applies mutatis mutandis to the subject matter of claims 23 and 24.

**2.0 Inventive Step (Article 33(3) PCT)**

The subject matter of claims 1 to 24 relate to the provision of parenteral formulations comprising estramustine phosphate with a sulfoalkyl cyclodextrin and human albumin, wherein, the technical problem is the avoidance of ulcerative damage and thrombophlebitis at the site of the injection.

D2 which is considered as the closest prior art and teaches the use of alkylated cyclodextrins to reduce ulceration, resulting from extravasation when injecting cytotoxic compounds, differs from the subject matter of claims 1 to 24 in the type of cyclodextrin employed.

D3 teaches the use of sulfoalkyl ether cyclodextrins in order to inhibit crystal formation in cyclodextrin drug complexes made up of water insoluble drugs, but does not address the technical problem of the application as originally filed. Therefore, the subject matter of claims 1 to 24 is considered as to involving an inventive step.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/EP00/07679

**3.0 Industrial Applicability (Article 33(4) PCT)**

For the assessment of the present claims 23 and 24 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item VIII**

**Certain observations on the international application**

The units mg/m<sup>2</sup> in claim 4 and on pages 5 and 8 of the description cause a lack of clarity (Article 6 PCT).